EDITORIAL

To get around the immune system, nanoparticles are disguised as red blood cells

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ABSTRACT

One of the key goals in the field of cancer drug administration has long been the creation of nanoparticle platforms with lengthy in vivo circulation half-lives. Long-circulating nanoparticles can better target the tumour site through passive or active targeting processes. PEG, which surrounds the particles with a hydration layer and so resists recognition by the mononuclear phagocyte system, is the current gold standard for bestowing long-circulating characteristics. The body's own long-circulating organisms, Red Blood Cells (RBCs), have recently inspired a new technique for producing biomimetic nanoparticles. Using membrane components produced directly from RBCs, this approach disguises drug nanocarriers as self. This approach has been shown to extend the half-life of particles in the systemic circulation beyond that of PEGylated systems. The RBC membrane-coated nanoparticles represent a significant advancement in drug delivery technology and hold a lot of promise for therapeutic use. We discuss the relevance and unique characteristics of this nature-inspired nanoparticle technology, as well as our thoughts on its future prospects.

Key Words: *Immune system; Nanoparticles*

INTRODUCTION

Many intriguing advancements in the field of disease therapies have been fueled by the introduction of nanoparticle-based drug delivery methods. Improved pharmacokinetics, higher tumour accumulations, less systemic exposure and side effects, and better patient compliance are all advantages of nanoparticulate drug formulations over their free-drug equivalents in cancer therapy. An extended systemic circulation half-life, which requires the nanoparticles to elude acquisition by the Mononuclear Phagocyte System's (MPS) macrophages, is a key property that underpins these benefits. The introduction of 'stealth' nanoparticles has had a significant impact on nanoparticle medication delivery, particularly in the treatment of cancer. Many studies have shown that by taking advantage of the tumor's leaky vasculature, stealthy, long-circulating nanoparticles can better localise to their tumoral targets *in vivo*.

Numerous ways have been implemented to enable nanoparticle immune evasion as a result of recent advances in nanotechnology. PEG functionalization is currently the most extensively used immune evasion technique. The nanoparticles are hidden beneath a hydration layer by these hydrophilic polymers, which reduce immune clearance. When foreign entities circulate in the circulation, they are normally designated for absorption by the MPS through a process called opsonization. Water molecules cover particles functionalized with PEG orother hydrophilic polymers, making them undetectable to opsonins and macrophages. The use of PEG to extend the circulation half-life of nanoparticles has proven to be beneficial, with half-lives on the range of tens of hours compared to minutes for non-PEGylated nanoparticles. Despite the success of PEG and its broad acceptance, recent reports of an anti-PEG immunological reaction have piqued the curiosity of scientists and engineers to examine long-circulation solutions based on biological inspiration.

RED BLOOD CELL (RBC)-BASED SYSTEMS AS LONG-CIRCULATING DRUG CARRIERS

Several groups have used nature as inspiration to construct long-lasting medication carriers. RBCs, which are natural oxygen transporters that may stay in the bloodstream for up to 120 days, are an ideal system to emulate and exploit in this regard. RBCs, for example, have a very flexible shape that allows them to move through tight capillary networks and 'sieving organs' like the spleen and liver. This property has led to the development of extremely biconcave microparticles, demonstrated by Doshi and Merkel that mechanobiological mimicry of RBCs can increase particle elasticity and extend circulation periods. The immune-evasive functions of membrane proteins on RBC surfaces have also been the subject of recent advancements in molecular and cellular biology. A range of proteins located on the cell membrane have been discovered to facilitate the identification of homologous RBCs as self. CD47, for example, has been discovered as a self-marker on RBC surfaces that actively alerts macrophages and hinders their absorption. Other membrane proteins on RBC surfaces, such as C8-binding protein (C8bp), Homologous Restriction Protein (HRP), Decay-Accelerating Factor (DAF), Membrane Cofactor Protein (MCP), Complement Receptor 1 (CR1), and CD59, fend off the complement system's onslaught. A drug delivery system with these RBC-like surface features should be able to limit immune reaction by posing as self and so achieve extended systemic circulation, at least in principle.

It has been claimed that synthetic techniques to imitate the surface characteristics of RBCs have been developed. Tsai, for example, coupled CD47 to polystyrene beads and displayed promising macrophage uptake inhibition. Existing chemical conjugation strategies for nanoparticle functionalization, on the other hand, have difficulties duplicating the complicated protein chemistry of RBC membranes. Alternative efforts have looked at the usage of RBCs and their derivatives for medicinal chemical transport. In theory, drug carriers made from autologous RBCs would be completely biocompatible and have low immunogenicity.

RBC MEMBRANE-COATED POLYMERIC NANOPARTICLES

Hu et al. have created a novel drug delivery technology that combines nanoscale RBC membrane-derived vesicles with polymeric nanoparticles produced from FDA-approved polymer poly(lactic-co-glycolic acid) (PLGA). A PLGA core is surrounded by an RBC membrane-formed shell in the resultant nanoparticle, which has a core–shell configuration. This method has the potential to provide the administration of slow-releasing therapeutic payloads in vivo with a carrier circulation half-life beyond that of PEG by combining the benefits of RBC-based carriers with those of polymeric nanoparticles. In a few easy processes, the particles are created. The cores are first created via a nanoprecipitation process, in which PLGA in an organic solvent is carefully added to a miscible anti-solvent. Extruding 2 m wide RBC ghosts through a membrane with 100 nm holes produces RBC membrane-derived vesicles. The resultant polymeric cores and RBC vesicles are extruded together to mechanically induce RBC membrane adsorption and fusing onto nanoparticle surfaces. The resultant RBC membrane-coated nanoparticles

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were shown to have exceptional stability in Phosphate Buffered Solution (PBS) and Foetal Bovine Serum (FBS). Furthermore, the protein composition of the finished camouflaged particles was substantially equal to that of the RBC ghosts, showing that the preparation procedure preserved all of the membrane self-markers required for extended circulation. The particle core and membrane shell were shown to be co-localized after in vitro absorption by a cancer cell, a significant finding that further validated the integrity of the particles' core–shell structure. Finally, the circulation half-life of these camouflaged nanoparticles was investigated, which yielded possibly the most fascinating discovery. In a mouse model, these new RBC membrane-coated nanoparticles had an elimination half-life of 39.6 hours compared to PEG-coated nanoparticles, which had an elimination half-life of 15.8 hours. These findings suggest that incorporating a nanoparticle core into RBC membranes has a stabilising impact on RBC membrane-derived vesicles, avoiding the problems that have plagued earlier nanoscale RBC-derived carriers, which have substantially shortened their circulation lifespan.